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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUYNH, PHUONG N	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/716,842	Applicant(s) BRIESEWITZ ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2002; Aug 5, 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,21-26,30-34 and 36-38* is/are pending in the application.

4a) Of the above claim(s) *1-15 and 37-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-18,21-26,30-34 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. The request for a continued prosecution application (CPA) under 37 CFR 1.53(d) filed on 10/3/02 is acknowledged. 37 CFR 1.53(d)(1) was amended to provide that the prior application of a CPA must be: (1) a utility or plant application that was filed under 35 U.S.C. 111(a) before May 29, 2000, (2) a design application, or (3) the national stage of an international application that was filed under 35 U.S.C. 363 before May 29, 2000. *See Changes to Application Examination and Provisional Application Practice*, interim rule, 65 *Fed. Reg.* 14865, 14872 (Mar. 20, 2000), 1233 *Off. Gaz. Pat. Office* 47, 52 (Apr. 11, 2000). Since a CPA of this application is not permitted under 37 CFR 1.53(d)(1), the improper request for a CPA is being treated as a request for continued examination of this application under 37 CFR 1.114. *See id.* at 14866, 1233 *Off. Gaz. Pat. Office* at 48.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/3/02 has been entered.

3. Claims 1-18, 21-26, 30-34 and 36-38 are pending.

4. Claims 1-15 and 37-38 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected invention.

5. Claims 16-18, 21-26 and 30-34 and 36 are being acted upon in this Office Action.

6. Claim 31 is objected to because said claim depends on canceled claim 29.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "said drug target" in claim 21 has no antecedent basis in base claim 16 because the word "drug target" is not recited in claim 21.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 16-17, 21-22, 23, 24-25, 30-21, 30-33, 34 and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Pichon *et al* (Mole Pharmacology 51(3): 431-38; 1997; PTO 892).

Pichon *et al* teach a method for directing the biodistribution of a drug such as ODN-p-KDEL to an intracellular space such as the internal compartments containing the KDEL receptor, i.e. IC, the ER and the cis-Golgi apparatus (See page 434, Intracellular Localization, in particular). The reference bifunctional molecule consisting of a drug such as ODN which is a 25 mer polynucleotide and a targeting moiety such as KDEL that is linked through a linker group such as a thio-carboxymethyl group which forms a thioester bond between said drug and said targeting moiety (See age 432, Materials and Methods, in particular). The reference bifunctional molecule exhibits enhanced efficacy by 5 fold upon administration to a mammalian host such as human hepatoma HepG2 cells (See page 433, Results, Biological Effect, in particular). The reference drug target is a protein such as the KDEL receptor. The reference bifunctional molecule is administered as a pharmaceutical preparation to inhibit expression of specific genes within cells and as a therapeutic agent for HIV in human (See page 431 and references 10-11 therein, in particular). The reference bifunctional molecule ODN-p-KDEL is a small molecule such as 15 peptides in length, which inherently is less than about 5000 Daltons (See page 432, oligonucleopeptide, in particular). The reference targeting moiety binds to an endogenous biodistribution modulating protein such as the KDEL receptor, which is also an intracellular protein located in the IC, the ER and the cis-Golgi apparatus (See page 434, Intracellular Localization, in particular). Thus, the reference teachings anticipate the claimed invention.

11. Claims 16-18, 21-26, 30-34 and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO 95/10302 publication (April 1995, PTO 1449).

The WO 95/10302 publication teaches a method of modulating the biodistribution of any drug by administering to a mammalian host, a bifunctional molecule consisting of a drug moiety such as opiates (See page 13 line 12) either covalently or non-covalently linked (see page 13 lines 32-35 to a targeting moiety such as steroid binding protein, thyroxin binding protein (See page 3 lines 22-25, page 9 lines 4-7, in particular) or steroid such as estradiol wherein the targeting moiety "will be selected to bind to its complementary binding member", for example, the steroid will bind to the steroid binding protein which is an intracellular protein and a small molecule (See page 10, lines 35-36, in particular). The WO 95/10302 publication further teaches that the bifunctional molecule exhibits enhanced efficacy of the drug upon administration to the host because the relative long half life of the targeting protein mentioned above which extend the half life of the drug in circulation and one can also modulate the ultimate sites or (target the drug) and volume of distribution of the bifunctional molecule based on location, distribution of the targeting molecule (See page 10 lines 1-21, in particular). The bifunctional molecule is either connected by covalent bonds (without linking group) or non-covalent linkage via monoclonal antibodies or fragments thereof such as Fv, Fab, $F(ab')_2$ (See page 13 lines 32-35; page 14, line 20-23; page 15 lines 1-2, in particular) or via a linking group such as bis-sulfosuccinimidyl suberate (See page 18 lines 26-36, in particular). The bifunctional molecule exhibits reduced toxicity upon administration to the host by selectively delivering the drug such as opiate within the cells of the CNS to limit toxicity (See page 9, line 37, in particular) or extend the life-time of the drug by conjugated to serum albumin or Fc of the immunoglobulin (See page 33 line 10, in particular) or to facilitate the clearance of the drug from the blood stream or to extend the stimulation of an immunogen (See abstract, in particular). The drug target opiate receptor is a protein and the drug is targeted to an intracellular site since the steroid binding protein, and thyroxin binding protein are endogenous biodistribution modulating intracellular protein. The WO 95/10302 publication teaches a method of modulating the biodistribution of any drug by linking a drug to a targeting moiety and thereby modulating the volume of distribution of the drug to ovoid non-specific undesired side-effects (See Abstract, Summary of the Invention, in particular).

While the reference is silence with regard to compared the drug to a free drug control, it is inherent to compare to the control in order to establish the effectiveness of the biodistribution of the drug. The bifunctional molecule has a molecular weight of less than about 5000 Daltons

since the targeting moiety has a molecular weight of about 200 D to less than about 1000 D and the molecular weight of the drug (opiates) has a molecular weight of about 3000 D and the sum of both is less than about 5000 Daltons (See page 20 lines 29-33, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 8/5/02 have been fully considered but are not found persuasive.

Applicants' position is that the WO 95/10302 publication teaches a method of maintaining a drug in an extracellular space such as long-lived blood component, i.e. Albumin. (2) WO 95/10302 publication does not teach or suggest a method of directing a molecule to intracellular space, much less by using a bifunctional molecule in which the ligand component of the molecule binds to an intracellular protein. (3) claims 16 and 30 have been amended to recite a method for directing a drug to an intracellular site and that the ligand binds to an intracellular protein.

However, the WO 95/10302 publication teaches other binding (targeting) entity such as steroid Estrogen (See page 10, lines 35-36, in particular), TSH, LH, FSH or their agonist (See page 25, lines 17-19, in particular) wherein the targeting moiety "will be selected to bind to its complementary binding member", for example, the steroid will bind to the respective steroid receptor which is an intracellular protein (See page 10, lines 35-36, in particular). As such, the reference steroid receptors are specific biodistribution modulating protein that locates in the intracellular space such as the cytoplasm.

12. Claims 16-18, 21-26, 30-34 and 36 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No. 5,843,440 (Nov 1998, PTO 1449).

The '440 patent teaches a method of modulating the biodistribution of any drug by administering to a mammalian host, a bifunctional molecule consisting of a drug moiety (Fab fragment of anti-cocaine antibody) (See Abstract, column 2, lines 2-9) linked to a targeting moiety such as steroid vitamin D (See column 2, lines 41-67 bridging column 3 lines 1-10, in particular). Upon administering the bifunctional molecule to the patient, the reference targeting moiety such as Vitamin D will bind to the endogenous biodistribution modulating protein such as the steroid binding protein, which is an intracellular protein. The bifunctional molecule is either connected by covalent bonds (without linking group) or non-covalent linked via monoclonal antibodies or fragments thereof such as Fv, Fab, $F(ab')_2$, (See column 8 lines 10-13; column 6

lines 27-31, in particular) or via a linking group such as a sulfhydryl group (See column 8, lines 45-57, in particular). The bifunctional molecule has a molecular weight of less than about 5000 Daltons. The '440 patent further teaches that the therapeutic methods are applicable to a broad range of target agent such as Fab fragment of anti-RBC conjugated to a Fab fragment of anti-cocaine to reduced toxicity of the drug upon administration of to a host (See column 3, lines 11-12, column 11, lines 11-in particular). The '440 patent also teaches a method of extending the lifetime of the bifunctional molecule in the blood stream (thereby enhance efficacy) by linking the antibody binding fragment (Fv) that binds specifically to erythrocytes or albumin to a second targeting agent such as antibody fragment that binds specifically to targeting agent or drug (See claims 1-8 of '440, in particular). The bifunctional molecule is a pharmaceutical composition to be administered parenterally, intravascularly, intramuscularly, subcutaneously, or by transfusion (See column 9, lines 6-26, in particular). While the reference is silence with regard to compared the drug to a free drug control, it is inherent to compare to the control in order to establish the effectiveness of the biodistribution of the drug. The '440 patent teaches a method of modulating the biodistribution of any drug by linking a drug to a targeting moiety and thereby modulating the volume of distribution of the drug to ovoid non-specific undesired side-effects (See Abstract, in particular).

Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 8/5/02 have been fully considered but are not found persuasive.

Applicants' position is that the '440 patent teaches a method of maintaining a drug in an extracellular space such as long-lived blood component, i.e. Albumin. (2) WO 95/10302 publication does not teach or suggest a method of directing a molecule to intracellular space, much less by using a bifunctional molecule in which the ligand component of the molecule binds to an intracellular protein. (3) claims 16 and 30 have been amended to recite a method for directing a drug to an intracellular site and that the ligand binds to an intracellular protein.

However, the '440 patent teaches other bifunctional molecule where the targeting moiety such as LH, or vitamin D which are hormone (See column 5, line 64, column 2, lines 64-66, in particular) where the reference the targeting moiety will bind to the respective steroid receptors which are intracellular proteins.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 16-18, 21-26, 30-34 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over the WO 95/10302 publication or US Pat No. 5,843,440 (Nov 1998, PTO 1449) each in view of US Pat No. 5,830,462 (Nov 1998, PTO 1449).

The teachings of the WO 95/10302 publication and the '440 patent have been discussed supra.

The references teachings differ from the claimed invention only by size of the targeting moiety of bifunctional molecule.

The '462 patent teaches various targeting moiety using a ligand such as FK506 that are small in size and binds to the endogenous biodistribution modulating protein such as peptidyl prolyl isomerase (FKBP12) or FKBP receptor which is an intracellular protein (See column 22, lines 62-64, in particular). The '462 patent further teaches other targeting moiety such as cyclosporin A that binds to the cyclophilin receptor, the estrogen that binds with the estrogen receptor, the vitamin D that binds to the vitamin D receptor with high affinity (See column 22 lines 66-67 bridging column 23, line 1-27). The reference targeting moiety such as FK506 is typically being at least about 150 D and few than about 5 kD, usually fewer than about 3 kD (See column 22, lines 62-64, in particular). The '462 patent teaches a bifunctional targeting domain such as FKBP12 ligand fused to a tryrosine kinase CD3ζ (See Fig 2, in particular) or FK506 fused to DNA binding domain (Gal4) (See Abstract, Fig 2, column 17, line 14; column 21 line

23-26, in particular) or Fas antigen receptors that is linked to FKBP12 which is capable of binding to the FK506 type moiety (See column 23 lines 17-20, claims 34-42, 47-51 and 109-112 of '462, in particular). The '462 patent further teaches that these moiety are linked together through a linking group (See column 24, lines 17-24, column 25, line 28-35, in particular). The '462 patent further teaches a pharmaceutical composition (See column 6, line 63-67 bridging column 7 lines 1-16, in particular). The '462 patent also teaches chimeric protein can be target to a specific location by adding a signal sequence from the vesicle or golgi or ER, for example (See claim 42 of '462, in particular). The '462 patent teaches the advantages of cyclosporin A2 and FK506 are they bind to their receptor with high affinity Kd $\leq 10^{-8}$ M (See column 23, line 11, in particular) and like FK1012s, it is neither immunosuppressive nor toxic (See column 27, lines 65-66, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the estradiol targeting moiety of the bifunctional molecule as taught by the WO 95/10302 publication or the steroid vitamin D targeting moiety as taught by the '440 patent for the FK506 that binds to FKBP12 or cyclosporin A that binds to the cyclophilin receptor with high affinity as taught by the '462 patent for a method for directing the biodistribution of any drug to an intracellular space upon administration to a host as taught by the WO 95/10302 publication, and the '440 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. While the reference is silence with regard to compared the drug to a free drug control, it is within the purview of one ordinary skill in the art to establish the effectiveness of a drug by comparing to the control.

One having ordinary skill in the art at the time the invention was made would have been motivated with a reasonable expectation of success to substitute because the '462 patent teaches that targeting moiety such as FK506 binds to FKBP12 with high affinity Kd $\leq 10^{-8}$ M (See column 23, line 11, in particular); cyclosporin A binds to the cyclophilin receptor with high affinity (See column 27, lines 52, in particular) and like FK1012s, it is neither immunosuppressive nor toxic (See column 27, lines 65-66, in particular).

Applicants' arguments filed 8/5/02 have been fully considered but are not deemed persuasive.

Applicants' position is that (1) the '462 patent teaches targeting of chimeric protein already present in the host, not of a drug moiety administered to the host. Nowhere in the patent

is directed to methods of modulating of biodistribution of a drug. The '462 patent is directed to a system in which engineered chimeric fusion proteins present in a subject are brought together by an administered bifunctional chemical inducer of dimerization to cause a desired effect that only occurs when the two chimeric proteins are brought together. (2) There is no motivation among the references for one to modify the primary references to target to an intracellular protein because no utility do so is provided. It would defeat the purpose of the primary references to swap out the long lived blood component and it would not accomplish the purpose of the secondary reference because such a substitution would not result in the desired dimerization of the chimeric proteins.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the '462 patent teaches various targeting domain such as cytoplasmic domains (See column 17, line 14, in particular), cellular targeting domains (See column 19, lines 49, bridging column 20, in particular). These cellular targeting domains such as FK506 binds to FKBP12 with high affinity Kd $\leq 10^{-8}$ M (See column 23, line 11, in particular); cyclosporin A binds to the cyclophilin receptor with high affinity (See column 27, lines 52, in particular) and like FK1012s, it is neither immunosuppressive nor toxic (See column 27, lines 65-66, in particular). The WO 95/10302 publication teaches a method of modulating the biodistribution of any drug by administering to a mammalian host, a bifunctional molecule consisting of a drug moiety such as opiates (See page 13 line 12) either covalently or non-covalently linked (see page 13 lines 32-35 to a targeting moiety such as steroid binding protein, thyroxin binding protein (See page 3 lines 22-25, page 9 lines 4-7, in particular) or steroid such as estradiol wherein the targeting moiety "will be selected to bind to its complementary binding member", for example, the steroid will bind to the steroid binding protein which is an intracellular protein and a small molecule (See

page 10, lines 35-36, in particular). The '440 patent teaches a method of modulating the biodistribution of any drug by linking a drug to a targeting moiety and thereby modulating the volume of distribution of the drug to ovoid non-specific undesired side-effects (See Abstract, in particular). The WO 95/10302 publication teaches a method of modulating the biodistribution of any drug by linking a drug to a targeting moiety and thereby modulating the volume of distribution of the drug to ovoid non-specific undesired side-effects (See Abstract, Summary of the Invention, in particular).

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

18. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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